REMARKS

Reconsideration of this application is requested. This application contains claims 1-22 pending and under consideration. These claims have been rejected under 35 U.S.C. 103(a) "as being unpatentable over Spanier et al. (U.S. Patents 5011679 and 5114704) in view of Witt et al. (U.S. Patent 6350438) and Miyake et al. (U.S. Patent 4913895) taken with Glandorf (U.S. Patent 5820853) and further in view of Perlberg et al. (U.S. Patent 5223643)." In light of the following remarks, it is believed that this rejection is addressed and overcome. Allowance of the application is requested.

The Applicant has discovered and demonstrated in working experimental that animal chew products that incorporate a combination of cetyl pyridinium chloride and sodium tripolyphosphate are highly effective in reducing the incidence of calculus, gingivitis and mouth odor when fed to dogs. In particular, in Example 2 of the application, a clinical experiment is described in which a double blind, crossover study was conducted comparing three regimens, one of which involved the use of the inventive impregnated rawhide. Four-week test periods demonstrated that the inventive two product led to substantial reductions in dental plaque and dental calculus. Furthermore, as reported in Example 2, the inventive combination was effective to reduce gingivitis at clinically and statistically significant levels, and moreover led to nearly a 20 percent reduction in mouth odor in the treated dogs. Accordingly, the Applicant in the present application has discovered a highly effective combination of actives in a chew product for improving the oral health of animals. These benefits were demonstrated in a clinical study administered by trained and established clinical examiners.

In order to render a claimed invention obvious under the standards of 35 U.S.C. 103, a combination of references must lead one of skill in the art to make the claimed combination with an expectation of success in its use. None of the references cited in the Office Action reflects any work in which cetyl pyridinium

chloride and sodium polyphosphate were combined in a chew product, much less tested on animals such as dogs, to determine whether a combination would be effective in improving the oral health of the animals. On the other hand, as noted above, the Applicant made and clinically tested such chew products and discovered that they performed unexpectedly in reducing dental calculus, dental plaque, gingivitis and mouth malodor.

Several of the secondary references cited in the Office Action describe developments having particular application in oral care products for human use and extend, by discussion, the potential use of the systems to animals such as dogs without providing any data to support that supposition. Such extension is dubious. It is well known that the composition of the calculus (tartar) formed in humans is significantly different from that formed in dogs. See, Driessens, FCM; Verbeeck, RMH, Possible Pathways of Mineralization of Dental Plaque. pp. 7-17 in *Recent Advances in the Study of Dental Calculus*, (proceedings of workshop/conference held in The Netherlands, November 6-9, 1988). JM ten Cate, Editor, IRL Press, 1989.

In humans the results of a series of studies indicated that calculus consists of a variety of calcium phosphates; the prevalence (in %) of these different calcium phosphates is as follows:

Calcium hydroxyapatite	93 - 100
Whitlockite (tricalcium phosphate	65 – 86
Octacalcium phosphate	94 – 95
Brushite (dicalcium phosphate)	14 - 44

As noted, regardless of the variation in composition between patients and samples, only calcium phosphates make up the mineral component of human calculus. See, Tovborg Jensen, A; Danø, M., *Crystallography of Dental Calculus and the Precipitation of Certain Calcium Phosphates*, J Dent Res 33:741-750, 1954; Forsberg, A., Lagergren, C, Lonnerblad, T., *Dental Calculus*, Oral Surg

13:1051-1060, 1960; Rowles, SL., *Biophysical Studies on Dental Calculus in Relation to Periodontal Disease*, Dent Pract Dent Rec 15:207, 1964; Schröder, HE, Baumbauer, HU, *Stages of Calcium Phosphate Crystallisation During Calculus Formation*, Arch Oral Biol 11:1-4, 1966; Ölzner, W, Hesse, A, Tscharnke, J, Schneider, HJ, *Struktur und Aufbau Menschlichen Zah*nsteins, Deut Stomatol 23:8-16, 1973; Sundberg, M, Friskopp, J., *Crystallography of Supragingival and Subgingival Calculus*, Scand J. Dent Res 93:30-38, 1985; and Legeros, RZ, Shannon, IL, *The Crystalline Components of Dental Calculi: Human vs. Dog*, J Dent Res 58:2371-2377, 1979.)

In contrast, calculus formed in dogs consists almost entirely of calcium carbonate (calcite) with only a trace of calcium phosphate (present as calcium hydroxyapatite). The reasons for these differences in composition between human and dog calculus are attributed to major differences in the composition and pH of the saliva. Human saliva is supersaturated with respect to apatite with high concentrations of calcium and phosphate and low concentrations of carbonate. In contrast, the saliva of dogs contains very high concentrations of carbonate and very low concentrations of phosphate. Comparative molar ratios of carbonate to phosphate concentrations in saliva are as follows:

Humans	< 1 (range of 0.1 – 0.3)
Dogs	>> 150 (range 180 - 1500

Similarly, there are highly significant differences in the normal pH of the saliva of humans and dogs. See, Driessens, FCM, et al., supra. The normal resting pH of saliva in humans is 6.8 while that of the dog is 8.0. As noted with phase diagrams by Driessens et al., these differences are very significant and, coupled with the differences in the composition of saliva between the two species, explain why there are such great differences in calculus compositions.

Considering these differences in calculus composition, saliva composition and saliva pH between humans and dogs, White et al. have noted that the use of

a rat model consistently predicted anti-calculus systems that are effective in humans while the use of the dog for this purpose was questioned since the mineral in rat calculus consists of calcium phosphates while that of the dog is calcium carbonate. See, White, DJ, Bowman, WD, Nancollas, GH, *Physical-Chemical Aspects of Dental Calculus Formation and Inhibition: in vitro and in vivo studies*, pp. 175-188 in Recent Advances in the Study of Dental Calculus (proceedings of workshop/conference held in The Netherlands, November 6-9, 1988), JM ten Cate, Editor, IRL Press, 1989. Thus, the extrapolation of assumptions of the efficacy of anti-calculus agents or systems from humans to dogs without data to support the extrapolation is unjustified.

More specifically as to the references cited in the rejection, Spanier et al. teach specifically the use of a pyrophosphate instead of any other organic phosphate compounds. Nonetheless, the Office Action states there would have been motivation from the combination of Spanier et al. and Witt et al. to replace the pyrophosphate of Spanier et al. with the tripolyphosphate listed among a multitude of other potential additives in Witt et al. The thrust of the teachings of Witt et al. is to use certain materials containing chlorite ion. From these disparate lists, it is posited in the Office Action that one would be guided to select tripolyphosphate and cetyl pyridinium chloride, and inject these into the teachings of Spanier et al. There is no compelling teaching that these should be selected for combination in the Witt et al. formulation, much less injected into the teaching of another reference that directs to use of different materials. Also, consistent with the discussion above, much of the teaching of Witt et al. is directed to compositions particularly for human use. No compositions were made or tested on dogs or any other animals. As noted, the chemical composition of the calculus that occurs in humans and animals is distinctly different and the extrapolation of formulations that perform effectively in one cannot properly be made to the other.

The Miyake et al. reference is relied upon in the Office Action for certain teachings about the use of polyphosphates for inhibiting caries in animal tests or

the use of water-soluble phosphate for inhibiting the formation of calculus. Miyake et al. do note the report in J Dent Res 43: 1123-1136 as to polyphosphates. This report is a literature review of the effect of dietary phosphates on the incidence of dental caries which indicates that orthophosphates and metaphosphates are effective in preventing dental caries in rats. However, caries is a disease associated with acidic pH values in dental plaque and decalcification of the underlying enamel while calculus is associated with elevated pH values and the precipitation of calcium phosphates in dental plaque. Further, it is well established that dental caries in quite rare in many animals such as dogs, while they still form calculus; the reasons cited for the failure of dogs to develop dental caries include: (a) the conical shape of the teeth; (b) higher salivary and plaque fluid pH values; (c) differences in normal oral flora with fewer organisms responsible for caries; (d) less fermentable carbohydrates in their diet; and (e) lower levels of salivary amylase to ferment dietary starches retained in the mouth.

The Office Action also notes that portion of the Miyake et al. reference that states "...and also possess antibacterial activity against Streptococcus mutans and Diphtheroids (e.g. Arch. Oral Biol. Vol. 27, p 809-816, 1982 and Infection and Immunity, Vol. 1, p. 604-606, 1970)." The first-cited article demonstrated that various phosphates exerted varying amounts of antibacterial activity against various strains of Streptococcus mutans (the microorganism primarily responsible for the development of dental caries) and the investigators suggested that the anticariogenic activity of these phosphates might be due to this effect on S. mutans. Similarly, the second-cited article confirmed the effects of phosphates, especially trimetaphosphate, on S. mutans but questioned the effect on Diphtheroids.

It is important to note that these citations are not related to the formation or prevention of calculus. It is also important to note that their observations were made in hamsters and laboratory tests focusing on the use of phosphates to prevent dental caries, not calculus formation. Moreover, there are significant

differences in the microbial composition of the oral flora of dogs and humans. In humans, S. mutans is the microorganism responsible for the initial formation of dental plaque and the development of dental caries. However, this particular organism (like other microbes responsible for the development of dental caries such as Lactobacillus acidophilus) is rarely found in dogs, and there are pronounced differences in the composition of the oral flora in dogs as compared to humans. See, Hennet, P. Periiodontal Disease and Oral Microbiology, Manual of Small Animal Dentistry, DA Crossley and S Penman, Editors, Chapter 11, pp. 105-113, British Small Veterinary Association publications, United Kingdom, 1995.

The Office Action also quotes Miyake et al. in stating that "Furthermore, Arch Oral Biol, Vol 15, p 893-896 (1970) discloses the effectiveness of a water soluble phosphate against the formation of calculus." This cited report used an in vitro model that is designed to form calcium phosphate mixtures similar to those found in human calculus to evaluate the effect of pyrophosphate and hexametaphosphate on the formation of these calcium phosphates. The investigators reported a significant decrease in the precipitation of calcium phosphates with the addition of pyrophosphate and hexametaphosphate but doubted if the additives would be effective in humans since the addition of saliva decreased the impact due to the action of phosphatases. No data were developed regarding the impact of these agents on the formation of calcium carbonate, the mineral component of calculus in dogs.

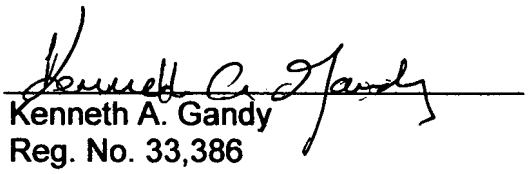
The Office Action also cites Glandorf et al., U.S. Patent No. 5820853, and states that it teaches the combination of polyphosphates with cetyl pyridinium chloride. However, Glandorf et al. '853 does not teach such a combination. It is believed that the Office Action intended to refer to Glandorf et al., U.S. Patent No. 6,251,216 on this point. However, Glandorf et al. '853 is directed to dual phase dentifrice compositions with antimicrobial activity provided by stannous ions, mentioning that tripolyphosphate may be included. In vitro tests are presented to predict impact in humans, although no actual test data in humans

are presented. As noted above, the authors have written in an extension of the systems for use in dogs; however, no tests were conducted and no data are presented.

The Perlberg et al. reference was relied upon in the Office Action for its teachings relative to a rawhide formulation made from chopped bits. Perlberg et al. teach only the use of an antimicrobial agent as a preservative to prevent the growth of mold and bacterial decomposition of the rawhide. Accordingly, the teachings of Perlberg et al. add nothing to the other references to render obvious the use of the claimed combination of materials in an animal chew product.

In summary, in order to render the present claims obvious, the combination of references must lead one of skill in the art to make the claimed combination with an expectation of success in its use. In the present case, the combination of references relied upon fails to do so. Therefore, reconsideration and allowance of this application containing claims 1-22 is requested. The Examiner is invited to contact the undersigned attorney by telephone if there are any questions about this submission or if there are other matters that may be handled in that fashion to expedite the allowance of this application.

Respectfully submitted,

By 

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